Positron emission tomography in urologic oncology

de Jong, IJ

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CHAPTER 7

$^{11}$C-CHOLINE POSITRON EMISSION TOMOGRAPHY FOR THE EVALUATION AFTER TREATMENT OF LOCALIZED PROSTATE CANCER.

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ABSTRACT

RATIONALE:
The evaluation of the efficacy of the treatment of men with prostate cancer is largely based on post treatment levels of PSA. An increase in PSA or biochemical recurrence is the first sign of recurrent disease and precedes a clinically detectable recurrence by months to years. Digital rectal examination and conventional imaging techniques are not sensitive to detect a local recurrence. A metabolic imaging technique, which is not dependent on anatomical distortions, could be of use. In this study we investigated $^{11}$C-choline-positron emission tomography (CHOL-PET) for the evaluation after treatment of localized prostate cancer.

METHODS:
Thirty six patients with localized prostate cancer, treated by either radical prostatectomy ($n=20$) or by external beam radiotherapy ($n=16$) were studied with CHOL-PET. The results of PET were compared with the results of histology and with clinical follow up.

RESULTS:
Fifteen patients had no biochemical failure after therapy. CHOL-PET was true negative in 15/15 patients. Twenty-one patients had a biochemical failure. In twelve patients recurrent tumor was identified by CHOL-PET. In eleven patients the recurrent tumor was confirmed by biopsy or by bone scan. In nine patients with a negative CHOL-PET scan, no recurrent tumor could be proven clinically, by biopsy nor during follow up.

CONCLUSION:
CHOL-PET is a feasible technique for evaluation of treatment with radical prostatectomy or external beam radiotherapy for localized prostate cancer. Confirmatory studies are needed to determine the efficacy of CHOL-PET as compared to other imaging techniques.

INTRODUCTION

Tumor recurrence after treatment for localized prostate cancer is first indicated by an increase in the serum value of prostate specific antigen (PSA). It occurs in 30 -50% of the patients within ten years after radical prostatectomy$^{1,2}$, and is seen in up to 80% of the patients within ten years after external beam radiotherapy$^{3}$. The increase of PSA is the most sensitive tool for detecting recurrences but can not distinguish between a local, regional or distant recurrence. In order to improve the discrimination between local or distant recurrence, the PSA doubling time (in months) and PSA
velocity (in ng/ml/year) are also advocated\textsuperscript{4,5}. A doubling time of more than 10 months is more related to a local recurrence whereas a doubling time of less than 4 months is predominantly seen in patients with a distant recurrence according to Partin et al.\textsuperscript{5}

Both digital rectal examination (DRE) and conventional imaging techniques fail to detect a local recurrence in 50% of the cases\textsuperscript{6,7,8}.

As may be clear from the above, the detection of the site of recurrence of prostate carcinoma after local treatment is difficult. Palpation and the conventional imaging techniques applied are all based on localization of anatomical distortions and a minimum size of this anatomical distortion is needed to yield a positive signal. By the time of a detectable local mass already a high incidence of distant metastases can be present.

Improvement may be reached by employing a metabolic imaging technique rather than an anatomic imaging technique. In this respect positron emission tomography (PET) may play a role. However, the results on PET for the evaluation of treatment of prostate cancer using the glucose-analogue 2-\textsuperscript{18}F-fluoro-2-deoxy-D-glucose (FDG) showed no benefit\textsuperscript{9,10,11}. FDG-PET could not discriminate between postoperative scar, benign hyperplasia and recurrent carcinoma.

Carbon-11 labeled choline (CHOL) has recently been reported as a new radiopharmaceutical for PET imaging and staging of tumors\textsuperscript{12}. Choline is one of the components of phosphatidylcholine, an essential element of phospholipids in the cell membrane\textsuperscript{13}. Malignant tumors show a high proliferation and increased metabolism of cell membrane components leading to an increased uptake of choline\textsuperscript{14}. Because CHOL is not rapidly excreted in urine, CHOL-PET showed clear images of the pelvic region and of the prostate carcinoma and pelvic lymph node metastases\textsuperscript{15,16,17}.

In this study we investigated CHOL-PET for the evaluation after treatment with radical prostatectomy or external beam radiotherapy for localized prostate cancer.

**MATERIALS AND METHODS**

**PATIENTS**

Patients treated for a localized prostate cancer by either a radical prostatectomy or by external beam radiotherapy were eligible. All patients were without evidence of lymph node or distant metastases at the time of treatment (N0M0). Patients on adjuvant hormonal therapy within six months prior to this study were excluded.

From both treatment groups we selected patients with no biochemical evidence of disease. Next, patients with biochemical evidence of disease after radical prostatec-
tomy were identified by two consecutive rises of serum PSA. Patients with biochemical evidence of disease after radiotherapy were identified by three consecutive rises of serum PSA after nadir according to the American Society for Therapeutic Radiology and Oncology criteria. Patients were recruited prospectively and were informed about the purpose and hazards of the study both orally and in writing, and gave their written informed consent. Approval from the Hospital Medical Ethics Committee was obtained. A total of thirty six patients participated in this study.

**PATIENT EVALUATION**

All patients were evaluated clinically by digitally rectal examination. In patients with biochemical evidence of disease, additional imaging by MRI or CT and a bone scintigraphy was performed to identify distant metastases in patients with a PSA exceeding 5 ng/ml.

**RADIOPHARMACEUTICALS**

The CHOL was produced using a robotic system by the method described by Hara and co-workers. CHOL was produced with specific activities > 3700 GBq/mmol and dissolved in 4 ml of saline. The solution was isotonic, colorless and sterile with a radiochemical purity of > 95%.

**IMAGING PROTOCOL**

Prior to the PET study the subjects were fastened overnight with exception of water and their usual medication. The PET studies were performed using either an ECAT 951/31 or an ECAT Exact HR⁺ PET Camera (Siemens/CTI, Knoxville, TN, USA). A transmission scan was performed over three bed positions (10 minutes per position), covering the pelvis and lower part of the abdomen, immediately followed by intravenous injection of 400 MBq CHOL. Data acquisition was started at 5 minutes after injection over the same area for 7 minutes per bed position.

**IMAGE RECONSTRUCTION AND DATA ANALYSIS**

Attenuation-corrected images were made using an iterative reconstruction algorithm (ordered subset expectation maximization, OSEM). PET-images were analyzed by 2 independent experienced PET physicians, who were blinded for the clinical data. The location of each lesion was marked on case record forms.

**HISTOLOGICAL EXAMINATION**

Histology was studied on the biopsy specimens and on operation specimens after
pelvic lymphadenectomy. The operation specimens were processed according to standard methods. Primary histological diagnosis was made upon H/E stained sections with, if necessary, additional immunohistochemical staining to optimize the histological diagnosis.

**RESULTS**

**RADICAL PROSTATECTOMY GROUP**
The characteristics of the patients after radical prostatectomy, serum PSA values and tumor stage and grade are summarized in table 1. The CHOL-PET did not show uptake of choline above background activity in the pelvic region in eight patients with no biochemical evidence of disease. Clinical follow after the CHOL-PET study showed no biochemical evidence of disease in all eight patients.

The CHOL-PET showed an increased uptake of choline in five of the twelve (42%) patients with a biochemical recurrence. A local recurrence in the prostatic fossa was detected in three of these five patients. DRE was abnormal in only one patient but a local recurrence was found at transrectal ultrasound (TRUS) and proven after transrectal biopsy in all three patients. The CHOL-PET showed an increased uptake of choline in pelvic lymph nodes in four of these five patients. Lymph node enlargement was seen on CT in these four patients and lymph node metastases were proven after lymphadenectomy in all four patients. In one patient CHOL-PET identified bone metastases as well as a local recurrence. The bone metastases were confirmed by an abnormal bone scan in corresponding localization’s. Figure 1 shows the PET images of a patient with a local recurrence after radical prostatectomy, PSA 8.5 ng/ml. In the biopsy a recurrent prostate carcinoma, Gleason sum score 7. A lymph node metastasis in the right iliac region was also found (not visualized in the presented tomograms).

In seven patients with an elevated PSA of 0.9 to 4.5, CHOL-PET did not show uptake of CHOL above the background activity in the pelvic region. Neither DRE, TRUS, bone scan nor CT could identify local recurrence nor distant metastases in these seven patients. Clinical follow up after the CHOL-PET study showed no evidence of disease in these patients yet.

**EXTERNAL BEAM RADIOTHERAPY GROUP**
The characteristics of the patients after external beam radiotherapy, serum PSA and tumor stage and grade are summarized in table 2. The CHOL-PET did not show uptake of CHOL above the background activity in the pelvic region in seven patients with no biochemical evidence of disease. Clinical follow up after the CHOL-PET study showed no biochemical evidence of disease in all seven patients.
Table 1. Patient details and results in post radical prostatectomy patients.

<table>
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<th>Age (yr)</th>
<th>PSA 1 (ng/ml)</th>
<th>TNM stage (1997 th Ed.)</th>
<th>Interval (month)</th>
<th>PSA 2 (ng/ml)</th>
<th>¹¹C-choline PET scan</th>
<th>DRE</th>
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bNED = biochemically no evidence of disease. HORM = hormonal therapy, DRE = digital rectal examination, XBR = external beam radiotherapy, n.a. = not available, n.p. = not performed, PSA1 = preoperative serum PSA, PSA2 = serum PSA at entry study, PSA3 = serum PSA at follow-up after study.
Table 2. Patient details and results in post radiotherapy patients.

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DRE = digital rectal examination, n.a. = not available, n.p. = not performed, DOC = death by other cause, HORM = hormonal therapy, TRUS = transrectal ultrasound. PSA1 = preoperative serum PSA, PSA2 = serum PSA at entry study, PSA3 = serum PSA at follow-up after study.
Chapter 7

The CHOL-PET showed an increased uptake of CHOL in seven of the nine (78%) patients with a biochemical recurrence.

The CHOL-PET showed a focal increased uptake of CHOL in the prostate in six of these nine patients. DRE was abnormal in only one patient, TRUS identified a local recurrence in two other patients. In three of the six patients a local recurrence was proven after transrectal biopsy. Two patients with a suspected local recurrence could not be evaluated by transrectal biopsy, but local recurrence was identified on DRE in follow up in one patient.

The CHOL-PET showed an increased uptake of CHOL in pelvic lymph nodes in one patient. No lymph node enlargement was seen on CT in this patient but lymph node metastases were proven after lymphadenectomy. In one patient CHOL-PET identified bone metastases as well as a local recurrence. The bone metastases were confirmed by an abnormal bone scan in corresponding localization’s.

Figure 2 shows the PET images of patient number 12 after radiotherapy with a local recurrence, Gleason sum 7, in the right lobe of the prostate.

In two patients with an elevated PSA of 2.3 and 8.7 respectively, CHOL-PET did not show uptake of CHOL above background activity in the pelvic region. Neither DRE, TRUS, bone scan or CT could identify local recurrence nor distant metastases in

Figure 1. CHOL-PET images of patient nr 18 after radical prostatectomy with a local recurrence (arrow), Gleason sum 7, and a lymph node metastasis in the right iliac region (not visible in these tomograms).
In the evaluation of treatment for localized prostate cancer residual or recurrent disease is first indicated by an increase of the serum PSA value. After radical prostatectomy a biochemical recurrence at 10 year follow up is seen in 30-50% of the patients in series operated before the PSA era. In more recent series of radical retropubic prostatectomies which included preoperative PSA testing in 88% of the patients, a biochemical recurrence rate of 26 % at 10 year follow up is reported. After radiotherapy a biochemical recurrence is seen in up to 80% of the patients at 10 year follow up. Although PSA is the most sensitive tool for detecting recurrences, it can not distinguish between a local, regional or distant recurrence. Unfortunately, physical examination and conventional imaging techniques are not sensitive in the detection of recurrent disease. Digital rectal examination is normal in 50% of the patients with a local recurrence.
recurrence. Transrectal ultrasound and transrectal biopsies of the prostatic fossa both fail to detect about 50% of the local recurrences. MRI and CT scans are not sensitive enough in the detection of a local recurrence but can be used to identify lymph node metastases with a sensitivity of 30 - 80%. Thus, detection of the site of recurrence of prostate carcinoma after radical prostatectomy or after radiotherapy is difficult. Advanced imaging techniques as well as digital rectal examination are based on localization of anatomic distortions and need a minimum size of this anatomical distortion before it can be detected.

Improvement may be reached by employing an imaging technique based on metabolism rather than an anatomic imaging technique. In this respect, PET may play a role. So far, there are limited data available on the use of PET for the evaluation of treatment of localized prostate cancer. Hofer et al. reported on the detection of local recurrence after radical prostatectomy with FDG-PET. They presented seven patients with an increased PSA after radical prostatectomy with local recurrences, proven by biopsy in three patients. The uptake of FDG in the recurrent tumor was not different from the uptake in postoperative scar, BPH or in primary prostate cancer. Haseman et al. showed five negative FDG-PET scans in six patients with biopsy proven local recurrences. Sanz et al. reported in their study on the utility of FDG-PET in prostate cancer on ten patients with progressive disease after therapy. FDG-PET identified nodal metastases in two patients of which CT scan showed no enlargement of lymph nodes. In general, despite very good results in other malignancies, FDG-PET has not met the expectations in its use for the evaluation of treatment in both metastatic as in newly progressive prostate cancer.

In this study we investigated CHOL-PET as a non invasive method for the evaluation of therapy for localized prostate cancer. So far, CHOL-PET has been shown to visualize prostate cancer, both primary tumor and metastatic sites with good contrast but no data are available on the evaluation of treatment.
In our series of 36 patients, fifteen patients had no biochemical evidence of disease. CHOL-PET showed no uptake of CHOL in the pelvic region (true negative) in all sixteen patients.
In eleven patients with an increased PSA after radical prostatectomy, a local recurrence was proven by biopsy in three patients and lymph node metastases were proven after lymphadenectomy in four patients. CHOL-PET identified all lesions as did conventional imaging with TRUS and CT scan in these patients.
In seven patients with an increased PSA after radical prostatectomy between 0.9 – 4.9 ng/ml, CHOL-PET was negative. Although no proof of a recurrence was found by DRE, conventional imaging, biopsy nor clinical follow up in these patients so far, a
benign cause for a PSA increase after radical prostatectomy is extremely uncommon. This result is in corroboration with the experience reported by Kozerke et al. using CHOL-PET in two patients with increasing PSA < 2 ng/ml after radical prostatectomy. Both CHOL-PET and conventional imaging failed to detect a biopsy proven local recurrence in these patients. These false negative CHOL-PET scans could be for the small volume of recurrent disease in this early stage. Failure to detect small volume disease is a known limitation of PET as well as of conventional imaging. Although the intrinsic resolution of the PET-camera is around 5 mm, the signal-to-noise ratio (contrast) is also of importance in PET imaging. A low contrast will decrease the visualization whereas high contrast can lead to an increase of visualization, which may extend beyond the intrinsic resolution. A longer clinical follow up is needed to confirm the true state of the negative CHOL-PET scans in these five patients. Nevertheless, the failure to detect recurrent disease below the PSA level of 5 ng/ml could limit the clinical use of CHOL-PET after radical prostatectomy as the results of salvage therapy are restricted in patients with a PSA > 1.0 ng/ml.

In patients with an elevated PSA after radiotherapy, a local recurrence in six patients and bone metastases in two patients were identified correctly by CHOL-PET. A negative CHOL-PET scan in one patient with an increased PSA of 2.3 ng/ml is likely true negative as PSA further decreased at clinical follow up. A temporary rise in PSA after radiotherapy is a known clinical phenomenon and can lead to confusion, mimicking a recurrent carcinoma. The second patient with a negative CHOL-PET scan showed PSA progression on follow up with a PSA doubling time of > 24 months, indicative but no proof of a local recurrence. Confirmatory data after prolonged clinical follow up of these two patients are needed also to determine the true nature of these negative CHOL-PET scans.

Other metabolic imaging techniques have also been studied for the evaluation of treatment of prostate cancer. ¹¹¹ In labeled capromab pendetide (ProstaScint®, Cytogen Corp. Princeton, NJ, USA) is a monoclonal antibody directed against prostate specific membrane antigen, a glycoprotein which is expressed by the prostate epithelium and is up regulated in (metastatic) prostate cancer. The initial studies on the use of ¹¹¹ In-capromab pendetide in patients with an average serum PSA value of around 30 ng/ml show sensitivities of 50–90% for the detection of a recurrence. In a recent study in 255 patients after radical prostatectomy with PSA values not exceeding 4.0 ng/ml, ¹¹¹ In-capromab pendetide uptake was noticed in 185 patients (72%). In 78 (30.6%) patients a local uptake in the prostatic fossa only was observed. Clinical or histological confirmation of a local recurrence was obtained in 16% of the patients so far. So far, interpretation of the images obtained by ¹¹¹ In-capromab pendetide is difficult and specialized training is still required. False positive examinations occur for uptake of
the radioisotope in small bowel, rectum, bone marrow and bladder wall. More confirmatory data are needed to prove the clinical value of $^{111}$In-capromab pendetide.

We recognize the limitations of our feasibility study because of the number of patients studied and the limited follow up. As in previous studies about the evaluation of treatment of prostate cancer, imaging and histological proof of recurrence could not be obtained in all cases for both practical and ethical reasons. But, by the combined data, the evidence for tumor tissue could be obtained in eleven of twelve (92%) patients with a positive CHOL-PET. With longer follow up we expect to evaluate the negative CHOL-PET scans further, identifying any false negative cases in due course. Nevertheless, our first results suggest that the clinical potential of CHOL-PET after radical prostatectomy will not extend beyond conventional imaging techniques, indicated by the negative scans in patients with a biochemical recurrence in the PSA range to 5 ng/ml.

**CONCLUSION**

This study showed that CHOL-PET is a feasible technique for evaluation of treatment for localized prostate cancer by radical prostatectomy or by external beam radiotherapy. Confirmatory studies are needed to determine the efficacy of CHOL-PET as compared to other imaging techniques.

**REFERENCES**


